which the amino acid at the position corresponding to amino acid Gly 119 of bovine growth hormone is at least as large in volume as leucine.

160
~~161~~ (new). A cell transformed by the DNA molecule of claim 40, and which expresses said variant.

52

161
~~162~~ (new). A method of producing a mammalian growth hormone variant having growth hormone receptor antagonist activity, which comprises maintaining cells of claim 154 under conditions conducive to the expression of said variant.

REMARKS

1. Claim Overview

1.1. The Examiner is thanked for faxing us proposed claims on January 27, 2003, and for reviewing the draft amendment for discussion purposes faxed March 5, 2003. Initially, SPE Gary Kunz advised me that proposed claims 120-143 were allowable, and that the other claims were likely to be rejected if presented. I pointed out to him that proposed claim 158 differed from proposed claim 120 only in that it recited "mammalian" rather than "vertebrate".

We had presented both 120 and 158 in independent form because the Examiner's January 27 fax had given us mixed signals. On page 2, of the fax, the Examiner's proposed claim "2" recited "mammalian". However, on page 4 of the fax, the Examiner wrote:

> Claim 81 is almost identical to claim 107, which recites "vertebrate" instead of "mammalian". Claim 107 appears to be acceptable as written.

On the next page, she explained:

> If the specification only supports mammalian growth hormone, I think the claims should be limited to mammalian

> growth hormone, as opposed to vertebrate growth hormone (see claims 114, 116-117). I believe flounder is mentioned in the specification, so this may serve as a basis for vertebrate, if that is what Applicant prefers. Further dependent claims could limit the vertebrate down to mammalian, or a Markush of the listed species in the specification could be done.

Page 17, line 21 of the specification in fact refers to fish (flounder, yellowtail, tuna, salmon) and to birds (chicken). There are also generic references to fish and birds at P16, L16-28. For generic reference to "vertebrate", see, e.g., P17, L19, 26, 37; P18, L5.

It is clear that we satisfy the Examiner's criterion for claiming "vertebrate", and this was confirmed by SPE Gary Kunz on March 26.

Consequently, proposed claim 158 ("vertebrate") has been presented as new claim 120. Proposed claim 121 (nucleic acid is DNA) is dependent in new claim 120. New claims 122-126, reciting the substitution at "119", are identical to proposed claims 129-133 save that they are dependent on vertebrate GH mutant claim 121. New dependent claim 127, reciting "mammalian", is identical in scope to proposed claim 121.

Proposed claims 129-133 are now new claims 128-132. Proposed claim 122 is now new claim 133. Proposed claims 134-138 are unchanged.

New claim 139 is like proposed claim 129 except it is expanded to include the vertebrate GHs of proposed claims 159 and 160. In effect it is a Markush group based on P17, L20-22, except for the omission of human. The Examiner noted on page of her fax that the Cunningham proviso was needed only if

the claim covered human GH variants.

New claims 140-144 correspond to proposed claims 124-128. New claims 145-149 correspond to proposed claims 139-143.

New claim 150 corresponds to proposed claim 146. Like claim 120, it requires a mutation at the AA corresponding to bGH Gly 119, and at least 80% AA identical overall with the wild-type GH. It differs from new claim 120 as follows:

(1) it recites a variant of a mammalian GH rather than a vertebrate GH;

(2) it requires that the variant have an alpha helix which is at least 80% identical, but not completely identical,[1] to the alpha helix of said mammalian GH which corresponds to the third alpha helix of bovine GH; and

(3) it omits the Cunningham proviso (since limitation (2) renders it unnecessary).

According to Gary Kunz, the Examiner's concern was that this claim combined an overall sequence identity limitation with a third alpha helix sequence identity limitation. She questioned whether this combination of limitations was fairly conveyed.

We direct the Examiner's attention to P18, L6-10:

> Preferably, the polypeptide is at least about 50% homologous, more preferably at least 80% homologous, with bGH or hGH in the subsequence substantially corresponding to the third alpha helix (...of bGH, and more preferably over the entire length of the polypeptide.

Plainly, the combination of these two types of

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[1] It can't be completely identical because 119 is in the third alpha helix.

limitations was expressly contemplated.

New claims 151-157, dependent on 150, correspond to proposed claims 147-153, and clearly are proper if 150 is accepted.

New claim 158 corresponds to proposed claim 157; it excludes a proline substitution at bGH Gly 119. Since proline was specifically mentioned at P21, L13, it can be specifically excised. See In re Johnson, 194 USPQ 187 (CCPA 1977).

New claims 159 and 160 correspond to proposed claims 144 and 145. Claim 159 recites that the substitute AA is at least as large in volume as proline and claim 160 that it is at least as large as leucine. Both proline and leucine were tested and found to be efficacious.

A table of the volumes of all 20 AAs is set forth on P23. On page 20, lines 9-21 we explain our theory that the successful substitutions (Arg, Pro, Lys, Trp and Leu) operate by filling a "cleft" in the face of the helix. There is explicit basis for claim 159 at P21, L22-24: "more preferably by any amino acid which is at least as large as Pro (the smallest replacement amino acid known to result in a 'small' animal phenotype)".

Claim 160 makes the logical extrapolation that it is even more preferable that the replacement AA be at least as large as Leu (the second smallest successful replacement tested). Bear in mind that these AAs, by definition, would more completely "fill the cleft" than would any smaller AA, and that the successful replacement AAs included Trp (the largest of all 20 AAs).

New claims 161 and 162 correspond to proposed claims 154 and 155 and we believe they are completely noncontroversial.

USSN - 08/488,164

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claim 40 has been amended as follows:

40 (amended). The DNA molecule of claim [10] 121, further comprising a promoter operably linked to said coding sequence whereby said [polypeptide] variant may be expressed in a host cell compatible with said promoter.

Claims 10-31, 33, 34, 37, 39, 65-87, 99-106, 108 and 111-119 have been cancelled.

Claims 120-162 have been added.